GENERIC PHARMACEUTICAL INDUSTRY ASSOCIATION

1620 I Street, NW Suite 800
Washington, DC 20006
(202) 833-9070
FAX (202) 833-9612

Alice E. Till, Ph.D.
President

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm.1061
Rockville, MD 20852

Re: Supplements and Other Changes to an Approved Application [Docket No. 99N-0193]

Sir/Madam:

On behalf of the Science Committee of the Generic Pharmaceutical Industry Association (GPIA), I am submitting comments on "Supplements and Other Changes to an Approved Application", FR 64 (123), 34608, June 28, 1999. Separate comments were submitted to Docket No. 99D-0529 by GPIA on August 26, 1999 on the "Draft Guidance for Industry on Changes to an Approve NDA or ANDA".

GPIA is comprised of the manufactures and distributors of generic medicines (as well as the providers of technical services and goods to these firms). Many of our members will be directly impacted by implementation of the subject proposed rule, amending the agency's current regulations on supplements and other changes to an approved application.

We would appreciate your consideration of the following comments as this rule is finalized.

Section IV. A. Definitions: It is stated that a definition for "validate the effects of the change" is necessary to implement section 506A of the FD&C Act (which requires that a drug made with a manufacturing change may only be distributed after the applicant "validates the effects of the change.") The meaning of the phrase is clarified in a footnote in the draft guidance to industry (footnote 5, section IV, page 4). When the final rule is published, it should be emphasized in the regulations, or in the preamble to the regulations, that this phrase is *not* the same as CGMP validation. Alternatively, the agency should consider replacing "validate" with "assess", to avoid confusion.

Section IV.G. Other Information: Under proposed Sec. 314.70(e), an applicant may submit one or more protocols describing specific tests, validation studies, and acceptable limits to be achieved to demonstrate the lack of an adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug. Such protocols, or changes to a protocol, would

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be submitted as a supplement requiring prior approval from FDA prior to distribution of the drug. If the supplement is approved, the use of such a protocol in making the specified changes may justify a reduced reporting category for the change because of the reduced risk of an adverse effect. It is noted that this proposed requirement is provided for in current regulations under Sec. 314.70(g)(4) and 601.12(e).

We believe that the expanded use of comparability protocols (CP) may, indeed, further reduce the regulatory burden. We agree that by pre-clearing CPs, the agency can have greater assurance that the change is being properly evaluated and that there is, therefore, less potential for the change to have an adverse effect on the safety or effectiveness of the product. It is expected that if approved, such a protocol could justify a reduced reporting category. However, additional clarification is necessary. The agency should further extend the benefits of CPs by encouraging applicants to submit protocols in original submissions to the extent possible.

We also believe that mandatory limits on CP review times should be established, otherwise there may be less of an incentive for applicants to adopt this procedure. In a manner similar to the procedure developed for disseminating bioequivalence guidance information, CPs which have been reviewed and approved by the agency should be made available under the Freedom of Information Act. This practice will help promote harmonization within the agency with respect to post-approval change and may provide interested parties with guidance on the general submission requirements the agency expects to see. The future CP guidance should contain a sufficient level of detail on testing requirements.

Section IV. D and E. Changes Being Effected Supplements: It is noted that the proposed moderate changes that may be implemented by an applicant when FDA receives a supplemental application are similar to the regulations in current Sec. 314.70(c) and that they are expected to provide the same, or increased, assurance that the product made will have the characteristics that it purports, or is represented, to have. The proposed regulations for other moderate changes requiring supplement submission at least 30 day prior to distribution of the drug product made using the change are intended for changes in the product, production process, quality controls, equipment, or facilities that have a moderate potential to have an adverse effect on the product.

In the preamble to the final rule, the agency should further clarify the criteria to be used to distinguish between a 30 day CBE and an immediate CBE.

Section IV. C. Changes Requiring Prior Approval Supplements: Current SUPAC guidance documents allow for limited formulation changes to be submitted as "Changes Being Effected" supplements or annual report notifications. However, the proposed regulations are more restrictive in that under proposed Sec. 314.70(b)(2), changes in the qualitative or quantitative formulation of the drug, including inactive ingredients, or in the specifications in the approved application or license, except as provided in proposed 314.70(c) and 314.70(d), are considered major changes that require supplement submission and approval prior to distribution of the product made using the change. Proposed Sec. 314.70(b)(2)(i) should be amended to better reflect Sec. 506A(2) of the act, by clearly stating that these changes are considered major changes unless exempted by a guidance. In addition, as written, this section is in conflict with

proposed Sec. 314.70(d)(2)(ii) [deletion or reduction of an ingredient only intended to affect the color of a product - a change in the qualitative or quantitative formulation.]

We are pleased that the agency is proposing to retain the general requirement that an applicant shall make a manufacturing change in accordance with a guideline (guidance) notice or regulation that provides for a less burdensome notification of the change. As the agency notes, this is consistent with FDA's goal of ensuring that the least burdensome means of reporting changes are available. However, we believe one point must be clarified. The preamble to the proposed rule states that to the extent that the recommendations on reporting categories in the draft guidance entitled, "Guidance to Industry: Changes to an Approved NDA or ANDA", when finalized, are inconsistent with previously published guidance, such as the SUPAC guidances, the recommended reporting categories in such prior guidance will be superceded by this new guidance upon its publication in final form. CDER intends to update the previously published guidances such as SUPAC, to make them consistent with this new guidance. We wholly support the creation and use of guidance documents, and in this particular instance recommend that the SUPAC provisions relating to changes in the qualitative or quantitative formulation of the drug be retained. Any revisions to current guidance documents should not result in more burdensome requirements.

Section IV. F. Changes to be Described in the next Annual Report: Under proposed Sec. 314.70(d) the agency is proposing that any change made to comply with an official compendium *that is consistent with FDA requirements and provides increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency*, is to be described in the next annual report. This is overly restrictive and may result in a *greater* regulatory burden for industry. We believe that the agency should continue to allow annual report notification for *any* change made to comply with an official compendium, consistent with the longstanding statutory arrangement between the agency and the USP. The above highlighted section undermines the authority of the USP and NF as the official compendia and source of the standards of strength, quality and purity of many drug products, and should be dropped from the proposal. A recent example is the new monograph on OVI's in the USP, where ICH limits have been adopted. Some of the OVI limits have been tightened and some are now permitted in greater quantities. This type of change should be submitted in an annual report.

Furthermore, it is not known on what basis firms are to determine in a timely manner (i) which compendial changes are consistent with FDA requirements (unspecified), and (ii) which changes will provide increased assurance. These additional criteria clearly are not consistent with the agency's goal of ensuring that the least burdensome means of reporting changes are available.

The Generic Pharmaceutical Industry Association appreciates this opportunity to provide our comments on the proposed rule.

Sincerely,

Alice E. Till, Ph.D.
President

CC: E. Sheinin, FDA (via mail and e-mail)
N. Tantillo, Chair GPIA CMC Taskforce